Tipranavir (TPV, APTIVUS)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral solution: 100 mg TPV/mL with 116 International Units (IU) vitamin E/ml

Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose used for TPV is higher than that used for other protease inhibitors (PIs).

Pediatric dose (<2 years of age):
TPV is not approved for use in children <2 years of age.

Pediatric dose (2–18 years of age):
Body surface area dosing:
TPV 375 mg/m^2 + RTV 150 mg/m^2, both twice daily.
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily.

Weight-based dosing:
TPV 14 mg/kg + RTV 6 mg/kg, both twice daily.
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily.

Adult dose:
TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily.

Selected Adverse Events

- Rare cases of fatal and nonfatal intracranial hemorrhage (ICH)
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer TPV with food.
- TPV oral solution contains 116 IU of vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- TPV contains a sulfonamide component and should be used with caution in patients with sulfonamide allergy.
- Store TPV oral solution at room temperature 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store oral TPV capsules in a refrigerator at 2°–8°C (36°–46°F). Capsules can be kept at room temperature (maximum of 25°C or 77°F) if used within 2 months after the bottle is first opened.
- Use TPV with caution in patients who may be at risk of increased bleeding from trauma,

surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

- Use of TPV is contraindicated in patients with moderate or severe hepatic impairment.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate.
- **Dosing of TPV in patients with renal impairment:** No dose adjustment is required.
- **Dosing of TPV in patients with hepatic impairment:** No dose adjustment is required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- Tipranavir has the potential for multiple drug interactions.
- Before tipranavir is administrated, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities:

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Laboratory abnormalities associated with tipranavir use include elevated transaminases, cholesterol, and triglycerides (TGs).
- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of ICH.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/TPV.html).

Pediatric Use: Tipranavir is Food and Drug Administration (FDA) approved for use in children ≥2 years of age who are treatment experienced and infected with HIV strains resistant to more than one PI[1]. The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the burden of taking a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events that limit its use to patients with few treatment options. However, tipranavir is approved for use in children as young as 2 years of age and is available in a liquid formulation.

FDA approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of tipranavir/ritonavir in HIV-infected children (PACTG 1051/BI-1182.14)[2]. This study enrolled treatment-experienced children (with the exception of 3 treatment-naive patients) ages 2 to 18 years (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children in 3 age strata were randomized to 2 different doses of tipranavir/ritonavir: tipranavir/ritonavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg per m^2 body surface area (high dose, 57 patients) twice daily plus optimized background therapy (OBT). All children initially received the oral solution but patients who were 12 years or older and receiving the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily were eligible to switch to tipranavir capsules after Week 4. At baseline, resistance to all commercially available PIs was present in greater than 50% of patient isolates, and the tipranavir/ritonavir mutation scores increased with the age of the child[2]. At 48 weeks, 39.7% of patients receiving the low dose and 45.6% of patients receiving the high dose had viral loads <400 copies/mL. The groups did not differ in the percentage of patients who achieved viral loads <50 copies/mL. The proportion of patients with HIV RNA levels <400 copies/mL tended to be greater in the youngest group of patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 cell count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, side effects were similar between treatment groups. Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs due to adverse events. The most common adverse events were gastrointestinal (GI) disturbances; 37% of participants had vomiting and 24% had diarrhea. Moderate or severe laboratory toxicity (primarily increase in gamma glutamyl transpeptidase [GGT] and creatine phosphokinase [CPK]) was seen in 11% of children. Four patients (all in the low-dose group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus the high-dose group reached statistical significance ($p = 0.04$). In a multivariate model, three variables (listed in order) predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100,000 copies/mL. GIQ is calculated by dividing the tipranavir trough concentration by the number of tipranavir resistance conferring mutations genotyped from the patient's HIV strain. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, the high-dose of tipranavir/ritonavir has been recommended.

PKs of the liquid formulation at steady state were assessed[3]. For children ages 2 to younger than 12 years, tipranavir trough concentrations for pediatric patients receiving tipranavir/ritonavir 290/115 mg per m^2 body surface area were consistent with tipranavir trough concentrations achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children 12–18 years of age required a higher dose (375/150 mg/m^2 body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard tipranavir/ritonavir dose. Population PK analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age[3]. Based on these studies the final dose of tipranavir/ritonavir 375/150 mg/m^2 body surface area twice daily is recommended.

Vitamin E is an excipient in the tripranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir per ml of solution. The recommended dose of tipranavir (14 mg per kg body weight) results in a vitamin E dose of 16 IU per kg body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%)[2]. Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%[4].

References

1. Courter JD, Teevan CJ, Li MH, et al. Role of tipranavir in treatment of patients with multidrug-resistant HIV. *Ther Clin Risk Manag.* 2010;6:431-441.
2. Salazar JC, Cahn P, Yogev R, et al. Efficacy, safety and tolerability of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents. *AIDS.* 2008;22(14):1789-1798.
3. Sabo J, Cahn P, Della Negra M, et al. Population pharmacokinetic (PK) assessment of systemic steady-state tipranavir (TPV) concentrations for HIV+ pediatric patients administered tipranavir/ritonavir (TPV/r) 290/115 mg/m^2 and 375/150 mg/m^2 BID (BI 1192.14 and PACTG 1051 study team). Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI); February 5-9, 2006; Denver, CO. Abstract R136, Poster 687.
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